REMARKS

Claims 1, 3, 6, 7, 10, 11, 18, 19, 22, 23, 26-28 and 31-41 are pending in the application. Claims 35-38 were previously elected in view of the restriction requirement.

Response to rejection under 35 U.S.C. §112

Claims 35-38 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges:

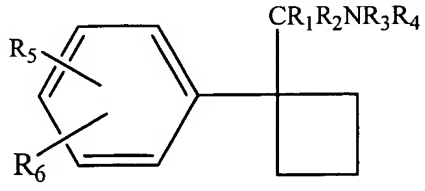
> There is insufficient descriptive support for the phrase, "derivatives of sibutramine". In addition, the instant specification does not describe what is meant by the phrase, "derivatives of sibutramine". Structural identifying characteristics of the phrase, "derivatives of sibutramine" are not disclosed. There is no evidence that there is any per se structure/function relationship between the phrase, "derivatives of sibutramine". The instant specification doe not provide an adequate written description for the phrase, "derivatives of sibutramine". Accordingly, these claims fail to comply with the written description requirement.

Applicant traverses the rejection.

Claim 35 is directed to a method for treatment of symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome including administering a pharmaceutically effective amount of sibutramine, sibutramine salts or derivatives of sibutramine which is a selective reuptake inhibitor for dopamine, serotonin and norepinephrine thereof to a human in need of such treatment. Sibutramine, sibutramine salts and derivatives of sibutramine

are distinguishable from other molecules and are described in the specification. Sibutramine means compounds of sibutramine hydrochloride monohydrate, more specifically N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride preferably in its monohydrate form, and enantiomers and analogues thereof, as described in U.S. Patent Nos. 4,746,680; 4,929,629; and 5,436,272. The specification directs one to refer to these patents for further details regarding the formulas, structure and methods of preparation (p. 15).

Additionally, a derivative is defined as a chemical compound that may be produced from another compound of similar structure in one or more steps, as in replacement of H by an alkyl, acyl or amino. See *Stedman's Online Medical Dictionary, 27th Edition*. As above discussed, the method of preparing and the structures of sibutramine, sibutramine salts and derivatives of sibutramine are defined on pages 12-13 of the specification. The analogues of sibutramine are further described in U.S. Patent No. 4,746,680 which discloses the sibutramine, salts and derivative as; compounds of formula I:



Formula I

in which R_1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, cycloalkylalkyl or optionally substituted phenyl; R_2 is H or C_{1-3} alkyl; R_3 and/or R_4 are H, formyl, C_{1-3} alkyl, C_{3-6}alkenyl, C_{3-6}

alkynyl, C_{3-7} cycloalkyl or R_3 and R_4 together with the nitrogen atom form a heterocyclic ring system; R_5 and/or R_6 are H, halo, CF_3, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring. Pharmaceutical compositions and processes for preparing compounds of formula I are further disclosed.

Further, U.S. Patent No. 4,929,629 describes N,N-Dimethyl-1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutylamine hydrochloride monohydrate, methods of preparation, salts and the addition of diluents and carriers. Furthermore, U.S. Patent No. 5,436,272 describes N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride, and the addition of diluents and carriers, as well as preparation thereof. Therefore, the derivative of sibutramine including the structure details and preparation methods are described in the above patent references referred to in the specification.

Additionally, the parent patent, U.S. Patent No. 6,323,242, Serial No. 09/204,124 and U.S. Patent No. 6,696,495, Serial No. 10/092,144, of which this application depends, has claims including "sibutramine, sibutramine salts or derivatives thereof" which were found described in such a way as to allow one skilled in the art to be appraised of what is to be encompassed by the invention.

Claims 35-38 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification to enable one skilled in the art to make and use the invention. The Examiner contends:

> **...the specification, while being enabling for sibutramine, does not reasonably provide enablement for the enablement of (1) derivatives of sibutramine nor (2) the plethora of compounds that are only known as possessing the pharmacological activity of being known as inhibitors of dopamine, serotonin, and norepinephrine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. (Action par. 11)**

This rejection is respectfully traversed. The above-arguments regarding sibutramine and derivatives of sibutramine equally apply herein. Further, the Examiner discusses the factors for enablement as seen in *In re Wands*, 8 USPQ2d 1400, (Fed. Cir. 1988). These factors include:

A. The nature of the invention;
B. The state of the prior art;
C. The level of one of ordinary skill;
D. The level of predictability in the art;
E. The breadth of the claims;
F. The amount of direction provided by the invention;
G. The existence of working examples; and
H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicant provides comments below addressing each of these factors.

A. The Nature of the Invention

Applicant agrees with the Examiner that the invention is directed to the method for treatment of symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome by administering selective reuptake inhibitors for dopamine, serotonin and norepinephrine. Further, claim 35 is directed to sibutramine, sibutramine salts or derivatives of sibutramine. Furthermore, the present invention is directed to the method of use of a known compound not to the structure of the compound itself.

B. The State of the Prior Art

Claim 35 is directed to sibutramine, sibutramine salts or derivatives of sibutramine. Sibutramine is known to inhibit the reuptake of serotonin, norepinephrine, and dopamine. Further, the chemical structure of sibutramine and its various derivatives and analogues are well known pharmaceutical compositions including sibutramine are currently marketed for obesity under the trademark Meridia® (Abbott). Sibutramine is also known to treat animals with neurological disorders such as epilepsy or conditions in which there is neurological damage (brain trauma and head injury) as seen in WO/95/21615. Applicant agrees with the Examiner that Young of WO 94/00114 fails to teach that sibutramine is a selective reuptake inhibitors for dopamine, serotonin, and norepinephrine and that it fails to teach the use of sibutramine as a treatment of symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome.

C. The Level of One of Ordinary Skill

The Examiner asserts that "the relative skill of those in the art is high." The Examiner, however, fails to define this assertion or provide any evidence to support this assertion. This appears to be the examiner's own belief as to what defines the hypothetical person skilled in the field of treatment of symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome. Moreover, the mere level of skill of one in the art is not by itself a definitive consideration in an analysis for a valid 35 U.S.C. 112, first paragraph, rejection.

D. The Level of Predictability in the Art

The Examiner contends the unpredictability in the art is very high. The Examiner further states that the physiological or pharmaceutical activity of the functional recitation of compounds, which are known to possess the pharmacological property of simply being known as a selective reuptake inhibitors for dopamine, serotonin, and norepinephrine prior to filing of the instant invention was an unpredictable art. Claim 35 is directed to a method for treatment of symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome including administering a pharmaceutically effective amount of sibutramine, sibutramine salts or derivatives of sibutramine which is a selective reuptake inhibitor for dopamine, serotonin and norepinephrine thereof to a human in need of such treatment.

Additionally, as above discussed, the parent patent and the referenced patents (p. 12 - 13 and 15 of specification) provide considerable direction and guidance in the specification which teach the preparation of sibutramine, sibutramine salts and derivatives of sibitramine. The use of the invention is further detailed in the specification pages 12-13, and 15 in addition to various case study examples (p 19-38). Thus, those skilled in the art could reasonably predict from the inventor's disclosure the scope of the claim.

E. <u>The Breadth of the Claims</u>

The breadth of the claims is not as the Examiner contends. For example, claims are not directed to a plethora of compounds.

The breadth of the claims is herein described. Claim 35 of the above-identified application is directed to a method for treatment of symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome including administering a pharmaceutically effective amount of sibutramine, sibutramine salts or derivatives of sibutramine which is a selective reuptake inhibitor for dopamine, serotonin and norepinephrine.

Claim 36 further limits claim 35 to the pharmaceutically effective amount including about 0.25 mg to about 45 mg per day.

Claim 37 further limits claim 35 to include delivering the pharmaceutically acceptable amount in a controlled or sustained release form.

Claim 38 further limits claim 35 to include an antiepileptic or anti-depressant medication.

F. The Amount of Direction Provided by the Inventor

Initially, the Examiner alleges there is no guidance in the way of enablement for sibutramine. Then the Examiner contends the specification provides enablement for sibutramine itself but not for derivatives or analogues thereof.

Claim 35 includes "sibutramine, sibutramine salts and derivatives of sibutramine, which is a selective reuptake inhibitor." Adequate guidance is provided for a skilled artisan in the specification (p. 12-13, and15) and the examples (p.19-38), as above-discussed and equally applicable here.

G. The Existence of Working Examples

Applicant agrees with the Examiner that the specification enables sibutramine and includes an example for treatment of symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome by administering sibutramine. Additionally, the specification as previously discussed enables sibutramine, sibutramine salts and derivatives thereof.

H. The Quantity of Experimentation Needed to Make and Use the Invention Based on the Content of the Disclosure

Examiner contends that one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the types and derivatives of compounds that are known in the art simply by the functional recitation of pharmacological property that acts as a selective reuptake inhibitors for dopamine, serotonin, and norepinephrine that would be enabled in this specification.

Applicant respectfully disagrees. Claim 35 is directed specifically to sibutramine, sibutramine salts or derivatives of sibutramine, which possess the recited reuptake inhibitor. The specification describes these compounds and directs one to refer to Patent Nos. 4,746,680; 4,929,629; and 5,436,272 for further details as to sibutramine derivatives and methods of preparation thereof, as above discussed and equally applicable here.

Applicant submits that in light of the above comments, the rejection under Section 112, first paragraph is obviated. Withdrawal of the rejection is respectfully requested.

Response to rejection under 35 U.S.C. §112, second paragraph

Claims 35-38 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner alleges:

> **The word "derivatives" fails to provide one skilled in the art with standard for determining what is embraced and encompassed with the word "derivatives". Without such clear information, one skilled is vaguely provided with information concerning what is embraced by the word "derivatives". Consequently, this claim is rendered vague and indefinite.**

Applicant respectfully traverses the rejection.

The identity of the derivative of sibutramine is sufficiently identified in the specification to enable one of ordinary skill in the art to practice the invention, as above-argued. Sibutramine, the structure and chemical formula are known in the art. The identity of the moieties intended to modify an art recognized chemical core, is present in the specification (pp. 12-13 and 15). The specification directs one to refer to U.S. Patent No. 4,746,680; 4,929,629 and 5,436,272 for additional description of the structure, chemical formulas and methods of preparation. The derivatives are described and easily attainable with the above-described information. Therefore, Applicant believes the rejection is obviated.

Claims 35-38 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner alleges:

> **It is unclear to the skilled artisan as to what specifically the instantly claimed compounds, sibutramine or sibutramine salts, are to be used therapeutically for or what is the intended benefit/risk ratio applicable for the claimed compound of sibutramine or sibutramine salts to a medical treatment? In addition, what is meant by the phrase, "effective amount"? Moreover, this ambiguous phrase does not clearly state what is to be therapeutically effected with a dose of sibutramine or sibutramine salts. This rejection could be obviated with the incorporation of the following phrase or equivalent "for treating reflex sympathetic dystrophy with the administration of sibutramine or sibutramine salts."**

Applicant respectfully traverses the rejection. However, in an effort to advance prosecution, claim 35 has been amended to include "for treating the symptoms of Reflex Sympathetic Dystrophy Syndrome or Complex Regional Pain Syndrome", in accordance with the Examiner's suggestion. Thus, the rejection is believed to be obviated in view the claim amendment.

Applicants' Response to Double Patenting Rejection

Claims 35-38 are rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 7, 14, 16, and 17 of U.S. Patent No. 6,323,242(herein '242). Specifically, the Examiner states:

> **Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instantly claimed**

> **subject matter as well as U.S. Patent No. 6,323,242 teach of treating pain with the administration of sibutramine and its salts and also with the addition of antiepileptic or anti-depressants. Clearly, one having ordinary skill in the art would have been motivated to utilize sibutramine for the treatment of pain in complex regional pain syndrome especially in view of the fact that U.S. Patent No. 6,323,242 teaches to the skilled artisan that it is known in the art that sibutramine is useful for the treatment of pain.**

Applicant traverses the rejection because claims 35 -38 are patentably distinct from claims 7, 14 16 and 17 of the '242 reference.

Independent claim 7 of the '242 reference is directed to a method for treatment of fatigue, pain, cognitive problems or sleep problems of fibromyalgia or chronic fatigue syndrome including administering a pharmaceutically effective amount of sibutramine, sibutramine salts or derivatives thereof to a human in need of such treatment.

Fibromyalgia and Complex Regional Pain Syndrome are two distinctly different conditions with different characterizations, diagnosis, symptoms and treatment. Fibromyalgia is a whole body condition which is characterized as a widespread musculoskeletal pain and fatigue disorder including back of your head, upper back and neck, upper chest, elbow, hips and knees, headaches, facial pain (www.mayoclinic.com/health/fibromyalgia). Fibromyalgia means pain in the muscles, ligaments and tendons of the fibrous tissue in the body. In contrast, Complex Regional Pain Syndrome is specific body condition which is characterized as a chronic condition

that usually affects your arms or legs. Rarely, the disease can affect other parts of the body (www.mayoclinic.com/health/complex-regional-pain-syndrome). '242 is directed to treating specific problems associated with Fibromyalgia being fatigue, pain, cognitive problems or sleep problems. However, the presently claimed invention is directed to the treatment of symptoms specific to Complex Regional Pain Syndrome. For example, symptoms of Complex Regional Pain Syndrome include intense burning pain, skin sensitivity, change in skin temperature, color texture, changes in hair and nail growth, joint stiffness, swelling and damage, muscle spasms, weakness and loss (atrophy), and decreased ability to move the affected body part (www.mayoclininc.com). The conditions are characterized different with different symptoms. In fact, the pain of each condition is different and effect different parts of the body. For instance, Fibromyalgia is a widespread pain affecting the whole body, however, Complex Regional Pain Syndrome which is an intense burning pain typically affecting arms or legs.

Further, the causes for Fibromyalgia and Complex Regional Pain Syndrome differ. For instance, Fibromyalgia may be caused by chemical changes in the brain, sleep disturbances, injury to the spine, or infection. However, Complex Regional Pain Syndrome may result from disturbances in the sympathetic nervous system which commonly flows from an acute problem, i.e. trauma to leg or arm. The causes of the conditions are not similar.

Furthermore, the treatment for Fibromyalgia and Complex Regional Pain Syndrome differ. For instance, treatments for Fibromyalgia include antidepressants, muscle relaxants, cognitive-behavioral therapy. In contrast, treatments for Complex Regional Pain Syndrome include application of heat and cold, physical therapy, sympathetic nerve-blocking medication, transcutaneous electrical nerve stimulation (TENS), biofeedback, and spinal cord stimulation. Even the treatment for each condition differs. Therefore, it would not be obvious that a treatment for Fibromyalgia would work for symptoms of Complex Regional Pain Syndrome. Fibromyalgia and Complex Regional Pain Syndrome are distinct conditions with different symptoms, diagnosis, causes and treatment.

Thus, claims 35-38 are patentable over claims 7, 14, 16, and 17 of U.S. Patent No. 6,323,242(herein '242). The double-patenting rejection is believed to be unwarranted and withdrawal of the rejection is respectfully requested.

Accordingly, Applicant believes the claims to be in condition for allowance and respectfully requests withdrawal of the rejections.

Should the Examiner have any questions regarding this response or wish to discuss this matter in further detail, please contact the undersigned counsel.

Respectfully submitted,

Anna-Lisa Gallo
Registration No.: 50,279
Attorney for Applicant(s)

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700